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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,339	08/15/2001	Luet Lok Wong	P02196USO	7723
26271	7590	12/16/2004	EXAMINER	
FULBRIGHT & JAWORSKI, LLP 1301 MCKINNEY SUITE 5100 HOUSTON, TX 77010-3095			PAK, YONG D	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/856,339

**Applicant(s)**

WONG ET AL.

**Examiner**

Yong D Pak

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 5 and 22-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5 and 22-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

This application is a 371 of PCT/GB99/03873.

The amendment filed on September 20, 2004, amending claim 1, has been entered.

Claims 1-3, 5 and 22-24 are pending. Claims 1-3, 5 and 22-24 are under consideration.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5 and 22-24 are rejected under 35 U.S. 112, first paragraph, because the specification, while being enabling for a P450 enzyme of SEQ ID NOs: 1 and 24, does not reasonably provide enablement for any P450 enzyme having 90% identity to an enzyme of SEQ ID NO: 1 or 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

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the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

The claims encompass any P450 enzyme having 90% identity to an enzyme of SEQ ID NO: 1 or 24. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of P450 enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two P450 enzyme. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of SEQ ID NO: 1 and 24 as a P450 enzyme but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue

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experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any P450 enzyme with 90% identity to the enzymes of SEQ ID NOS:1 and 24 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting P450 enzyme activity; (B) the general tolerance of P450 enzyme to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including P450 enzyme with an enormous number

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of amino acid modifications of the P450 enzyme of SEQ ID NOS: 1 and 24. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of P450 enzyme mutants and variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

### ***Response to Amendment***

The declaration under 37 CFR 1.132 filed on September 20, 2004 is insufficient to overcome the rejection of claims 1-3, 5 and 22-24 based upon Wong et al. applied under 35 U.S.C. 103 and Flitsch et al. applied under 35 U.S.C. 103 as set forth in the last Office action because: the declaration fails to overcome the rejections under 35 U.S.C. 103 for the following reasons.

The declaration argues that because the substrates recited in the present claims are significantly different from the substrates disclosed in the references of Wong et al. and Flitsch et al. and that the cited references cannot be used to predict whether or not the substrates recited in the present claims can be oxidized by a mutant P450 enzyme. Examiner respectfully disagrees. Both Wong et al. and Flitsch et al. teach a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of P450<sub>CAM</sub> and P450<sub>BM-3</sub> (pages 19 and 25). Sesquiterpenes and monoterpenes belong to the same family of molecules called terpenes, which contain

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the signature isoprene units. Thus, the substrates recited in the present claims and the substrates disclosed in the cited references are not significantly different. Further, because the substrates in the cited references and the substrates recited in the instant claims are structurally related, one of ordinary skill in the art would have expected other molecules from the family of terpenes to be substrates of the mutant P450 enzymes of Wong et al. or Flitsch et al. Since compounds similar in structure will have similar properties, the ability of the mutant P450 enzymes of Wong et al. or Flitsch et al. to act on other terpenes would not have been an unexpected result. Therefore, it would have been obvious to one having ordinary skill in the art to apply the teachings of Wong et al. and Flitsch et al. to other terpenes, such as sesquiterpenes.

### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 103***

Applicant's arguments filed on September 20, 2004 have been fully considered but they are not persuasive.

Claims 1-3, 5 and 22-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al.

Applicants argue that because the substrates recited in the present claims are significantly different from the substrates disclosed in the reference of Wong et al. and that the cited reference cannot be used to predict whether or not the substrates recited in the present claims can be oxidized by a mutant P450 enzyme. Examiner respectfully

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disagrees. Wong et al. teach a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of P450<sub>CAM</sub> and P450<sub>BM-3</sub> (pages 19 and 25). Sesquiterpenes and monoterpenes belong to the same family of molecules called terpenes, which contain the signature isoprene units. Thus, the substrates recited in the present claims and the substrates disclosed in the cited reference are not significantly different. Further, because the substrates in the cited reference and the substrates recited in the instant claims are structurally related, one of ordinary skill in the art would have expected other molecules from the family of terpenes to be substrates of the mutant P450 enzymes of Wong et al. Since compounds similar in structure will have similar properties, the ability of the mutant P450 enzymes of Wong et al. to act on other terpenes would not have been an unexpected result. Therefore, it would have been obvious to one having ordinary skill in the art to apply the teachings of Wong et al. to other terpenes, such as sesquiterpenes.

Claims 1-3, 5 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flitsch et al.

Applicants argue that because the substrates recited in the present claims are significantly different from the substrates disclosed in the reference of Flitsch et al. and that the cited reference cannot be used to predict whether or not the substrates recited in the present claims can be oxidized by a mutant P450 enzyme. Examiner respectfully disagrees. Flitsch et al. teach a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of P450<sub>CAM</sub> and P450<sub>BM-3</sub>



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(pages 19 and 25). Sesquiterpenes and monoterpenes belong to the same family of molecules called terpenes, which contain the signature isoprene units. Thus, the substrates recited in the present claims and the substrates disclosed in the cited reference are not significantly different. Further, because the substrates in the cited reference and the substrates recited in the instant claims are structurally related, one of ordinary skill in the art would have expected other molecules from the family of terpenes to be substrates of the mutant P450 enzymes of Flitsch et al. Since compounds similar in structure will have similar properties, the ability of the mutant P450 enzymes of Flitsch et al. to act on other terpenes would not have been an unexpected result. Therefore, it would have been obvious to one having ordinary skill in the art to apply the teachings of Flitsch et al. to other terpenes, such as sesquiterpenes.

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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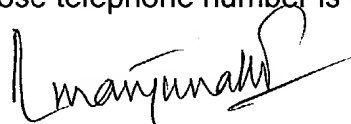
shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak  
Patent Examiner 1652

  
Rao Manjunath  
Primary Examiner 1652  
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